REMARKS

Claims 24-29, 39, 40, 44 and 45 are pending. Claims 1-23, 30-38, 41-43, 46 and 47 are cancelled herein without prejudice. Claims 24-29, 39, 40, 44 and 45 are amended. The amendments add no new matter.

Priority Documents:

The Office Action notes that certified copies of "some" of the priority documents have been received. In fulfillment of the requirement that certified copies of all priority documents be filed, Applicants submit herewith certified copies of United Kingdom priority applications GB 0119557.7, filed August 10, 2001, GB 0127917.3, filed November 21, 2001 and GB 0210740.7, filed May 10, 2002.

Objections:

The Office Action notes that in claims 24-29, 39-40 and 44, the word "stabilising" should be spelled "stabilizing." Applicants note that the instant application is based on (a CIP of) a PCT drafted in Great Britain, where the alternative spelling "stabilising" is correct. Nonetheless, Applicants have amended the spelling of the term as requested by the Examiner.

The Office Action notes that the term "FL-CD83" at line 17 of page 42 should be "FL-CDB3." Applicants have made the requested change herein.

Rejection under 35 U.S.C. §101:

Claims 24-29, 39 and 40 are rejected under 35 U.S.C. §101 as drawn to non-statutory subject matter. The Office Action states that "[t]he claims refer to a stabilizing molecule, which is not isolated or purified, and therefore it is in its natural state."

Applicants have amended independent claim 24 to recite "an isolated stabilizing molecule." Applicants submit that the amendment is sufficient to overcome the §101 rejection of claim 24 and claims that depend from it. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, Second Paragraph:

Claim 24 is rejected as indefinite under 35 U.S.C. §112, second paragraph for use of the phrase "a natural binding partner." The Office Action states:

> The phrase is indefinite, since the natural binding partner can encompass an indefinite number of biological/chemical compounds. The applicant defines in the specification "a natural binding partner" as a molecule that specifically binds to the native state of a given polypeptide in vivo in a wild-type cell or organism," however, this definition is not satisfactory because the specification does not further define the natural compound and it does not provide any specific examples or further guidance regarding its structure."

Applicants respectfully disagree.

Applicants submit that §112, second paragraph requires that the claim apprises one of skill in the art of its scope and, therefore, serves the notice function required by that section by providing clear warning to others as to what constitutes infringement of the patent. *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). It is important that definiteness be determined in terms of how one of skill in the art would construe the claim. *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1571 (Fed. Cir. 1983). Essential in this inquiry is whether one of skill in the art could, in view of the specification and knowledge in the art, interpret the metes and bounds of the claim so as to understand how to avoid infringement. *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

As defined in the specification, the term "natural binding partner" "refers to a molecule that specifically binds to the native state of a given polypeptide *in vivo* in a wild-type cell or organism." Applicants submit that one of skill in the art would be able to recognize what is and what is not a natural binding partner on the basis of this definition. This is what is required to satisfy the law. Applicants stress that there is no requirement under §112, second paragraph that, as alluded to in the Office Action, the claims encompass a definite number of any element. If one of skill in the art would recognize whether a given molecule is a "natural binding partner" – that is, is it a molecule that binds to the native state of a given polypeptide *in vivo* in a wild-type cell or organism? – the term is definite and the law is satisfied, despite the fact that a number of

other molecules might also fit this definition. Applicants respectfully request reconsideration and withdrawal of this rejection under §112, second paragraph.

Claim 26 is rejected under §112, second paragraph because "the Applicant refers to different mutations of p53 polypeptide, however there is no reference to the polypeptide's amino acid sequence. Applicants respectfully disagree.

Applicants have amended parent claim 25 to refer to "human" p53 polypeptide. Applicants submit that the amino acid sequence of human p53 is very well known in the art, as acknowledged in the Office Action (see page 5, lines 12-15 of the Office Action). Thus, there is no need for the claim to refer to a specific p53 amino acid sequence in order for one of skill in the art to recognize a human p53 mutant including a mutation, relative to the well known wild-type human p53, selected from R175H, G245S, R248Q, R249S, R273H, R282W and I195T as recited in claim 26. Not only is it clear to one of skill in the art what is the amino acid sequence of human wild-type p53, it is also clear whether a mutant of that p53 sequence has a mutation that deviates from the wild-type in one of the specific ways recited. In view of the amendment to parent claim 25 and the discussion above, Applicants submit that claim 26 is definite without need to refer to an amino acid sequence. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

Claims 27 and 45 are rejected under §112, second paragraph because there are no SEQ ID NOs assigned to the recited CDB3 peptide. Applicants have amended both claims 27 and 45 herein to refer to SEQ ID NO: 1. In view of the amendment, Applicants respectfully request withdrawal of this §112, second paragraph rejection.

The Office Action also rejects claims 27 and 45 because "the name of CDB3 must be spelled out." Applicants have amended claims 27 and 45 herein to delete the term "CDB3." Applicants submit that the amendment is sufficient to overcome this ground of rejection and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C.§102(b):

Naumovski et al.

Claims 24-29, 44 and 45 are rejected under 35 U.S.C. §102(b) as being anticipated by Naumovski et al. (1996, Mol. Cell. Biol. 16: 3884-3892). The Office Action states that the

Naumovski et al. reference teaches "the structure of Bcl2-binding protein ('Bbp') that specifically interacts with p53 protein in vivo, where the Bbp necessary (sic) requires for its binding to the p53 a specific ankyrin repeats (sic) and SH3 domain." The Office Action refers particularly to Figure 1, page 3886, and states that Figure 3, page 3887 shows binding of Bbp protein to p53, and that "Figure 6, page 3888, shows an amino acid sequence of Bbp, which contains REDEDEIEW amino acid sequence, as part of the SH3 domain necessary for binding of Bbp protein to p53." The Office Action states "[t]hat the REDEDEIEW amino acid sequence of Bbp protein is identical to the instant invention (claims 27 and 45)." The Office Action concludes that "[t]herefore, the claims are anticipated by Naumovski et al. because the REDEDEIEW amino acid fragment of Bbp protein is identical to claims 27 and 45 of the instant invention, and the amino acid fragment has the same function of binding p53 domain." Applicants respectfully disagree.

First, Applicants submit that the Naumovski et al. reference does not teach an isolated stabilizing molecule which binds to and stabilizes the native state of a polypeptide, but not a denatured state of the polypeptide, in which the stabilizing molecule binds to a site which at least partially overlaps a functional site of the polypeptide, and in which the stabilizing molecule does not consist of a natural binding partner of the polypeptide, as required by claim 24 as amended. More particularly, the Naumovski et al. reference does not teach a stabilizing molecule "in which the stabilizing molecule does not consist of a natural binding partner of the polypeptide." Applicants submit that, as described by Naumovski et al., 53BP2/Bbp is a natural binding partner of p53 and cannot, therefore, fall under the claims.

Second, Applicants submit that Naumovski et al. does not teach that 53BP2/Bbp is a stabilizing molecule – the reference may demonstrate the ability of 53BP2/Bbp to bind wild-type p53, but the reference does not teach or suggest stabilization of p53 by 53BP2/Bbp, particularly not by a molecule that at least partially overlaps a functional site of the polypeptide, as recited in claim 24.

With regard to claim 26, which the Office Action states "is included in the rejection because the structure of p53 is known and the mutations R175H, G245S, R248Q, R249S, R273H, R282W and I195T are well known in the prior art," Applicants also note that the

Naumovski et al. reference states that 53BP2/Bbp does not bind to mutant p53, which contradicts the explicit requirement of claim 26 that the polypeptide, bound to and stabilized by the claimed stabilizing molecule, be one of the recited p53 *mutants*.

Finally, Applicants submit that the Naumovski et al. reference does not teach the REDEDEIEW fragment recited in claims 27 and 45. The reference may teach the full length Bbp polypeptide and several truncated polypeptides that include REDEDEIEW as part of their sequences, but the reference teaches neither an REDEDEIEW fragment nor any activity associated with such a fragment.

In view of the above, Applicants submit that the Naumovski et al. reference does not anticipate independent claims 24 or 45 as amended or any of their dependent claims. Applicants respectfully request reconsideration and withdrawal of the §102(b) rejection over this reference.

Kopchick et al. (U.S. 5,681,809)

Claim 24 is rejected under §102(b) over Kopchick et al. (U.S. 5,681,809). The Office Action states that the Kopchick et al. reference teaches growth hormone receptor antagonists. The Office Action states that the GH antagonist is considered to be a stabilizing agent, which binds the GH polypeptide functional site. Applicants respectfully disagree.

Applicants submit that the Kopchick et al. reference describes GH antagonists derived by mutation of the GH polypeptide itself, and teaches that mutations of GH that stabilize the third alpha helix of the GH mutant result in a GH molecule with antagonist activity. However, the reference does not teach that an antagonist binds to and stabilizes the native state of the GH polypeptide. That is, while the reference teaches stabilization of a GH alpha helix by mutation, the reference does not teach that it is a GH mutant that binds to and stabilizes an alpha helix of a GH molecule, as would be required for this reference to anticipate claim 24 as amended.

In view of the above, Applicants submit that the Kopchick et al. reference does not anticipate claim 24. Applicants respectfully request reconsideration and withdrawal of this §102(b) rejection.

Rejection under 35 U.S.C. §102(e)

Winnacker et al. (U.S. 6,451,541)

Claims 24, 28 and 29 are rejected under 35 U.S.C. §102(e) as anticipated by Winnacker et al., U.S. 6,451,541. The Office Action states that the Winnacker et al. reference teaches chaperones Hsp60 that bind to prion protein PrPC. The Office Action states that Winnacker et al. also teach that prior art chemical chaperones, such as glycerol, trimethylamine N-oxide, and DMSO stabilize PrPC and prevent its conversion to PrPSc. From this, the Office Action concludes that claims 24, 28 and 29 are anticipated by the reference. Applicants respectfully disagree.

Applicants submit that Hsp60 as taught in Winnacker et al. is a natural binding partner of the prion protein PrP^c. That is, Hsp60, which is widely expressed, is taught to be "a molecule that specifically binds to the native state of a given polypeptide [PrP^c] *in vivo* in a wild-type cell or organism." As such, the claims specifically fail to encompass Hsp60 in its described role as a stabilizing molecule of PrP^c.

With regard to the so-called "chemical chaperones" referred to in the Office Action, Applicants submit that there is no teaching that any molecule among the "chemical chaperones" described in the Winnacker et al. reference "binds to and stabilizes the native state of a polypeptide, but not a denatured state of the polypeptide," as required by the claims. Similarly, there is not any teaching that a "chemical chaperone" as described "binds to a site which at least partially overlaps a functional site of the polypeptide" as required by the claims. As such, Applicants submit that the Winnacker et al. reference cannot anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 24, 28 and 29 over the Winnacker et al. reference.

Rejection under 35 U.S.C. §103(a)

Claims 24, 39 and 40 are rejected as obvious under 35 U.S.C. §103(a) over a combination of Naumovski et al. in view of Nandabalan et al. (U.S. 5,977,311). The Office Action states that Naumovski et al. does not teach Bbp which is bound to a fluorophore, e.g., fluorescein. The Office Action cites Nandalaban as teaching that proteins are routinely labeled with a radioligand, such as fluorescent ligand, e.g., fluorescein, for screening purposes. The Office Action

concludes that it would have been obvious to one of skill in the art to label a stabilizing molecule of Naumovski et al. with a fluorescent ligand taught by Nandalaban. Applicants respectfully disagree.

Applicants submit that the Nandalaban et al. reference does not remedy the defects in the Naumovski et al. reference as discussed above. Specifically, Nandalaban et al. does not teach a stabilizing molecule "in which the stabilizing molecule does not consist of a natural binding partner of the polypeptide." Further, the Nandalaban et al. reference does not provide any teaching or suggestion that 53BP2/Bbp is a stabilizing molecule or that it specifically binds a target polypeptide "at a site that at least partially overlaps a functional site of the polypeptide," as required by claim 24. As such, Applicants submit that no combination of Naumovski et al. with the Nandalaban et al. reference can provide all necessary elements of claim 24 as amended herein. Thus, the cited combination of references cannot render obvious the invention of claim 24 or any claim that depends from it. Applicants respectfully request reconsideration and withdrawal of the rejection of these claims over the cited combination of Naumovski et al. and Nandalaban et al.

In view of the above, Applicants submit that all issues raised in the Office Action have been addressed herein. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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